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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/979,539	11/20/2001	Ira Pastan	15280-3951US	5936

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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 11/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/979,539	PASTAN ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8,10,12-16,21,27,31,33-37,41-50 and 69-89* is/are pending in the application.

4a) Of the above claim(s) *41-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8,10,12-16,21,27,31,33-34,41-50 and 69-89* is/are rejected.

7)☒ Claim(s) *35-37* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/6/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-5, 8, 10, 12-16, 21, 27, 31, 33-37, 41-50 and 69-89 are pending.

Claims 6-7, 9, 11, 17-20, 22-26, 28-30, 32, 38-40 and 51-68 are cancelled.

Claims 1, 12, 14-15, 27, 33 and 35-37 has been amended.

Claims 69-89 have been added.

Claims 41-50 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

2. Claims 1-5, 8, 10, 12-16, 21, 27, 31, 33-37 and 69-89 are under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. This Office Action contains New Grounds of Rejections.

Rejections/Objections Withdrawn

5. The objections to claims 7 and 63 are withdrawn in view of the cancellation of the claims.

6. The rejection of claims 1-6, 27-28, 51-54 and 60-61 under 35 U.S.C. 101 as being drawn to non-statutory subject matter as lacking the hand of man is withdrawn in view of the amendments to the claims.

7. The rejection of claims 1-21, 27-29, 31-40 and 51-59 under 35 U.S.C 112, second paragraph, as being indefinite in the recitation of "having at least 5 times

higher binding affinity for an antigen bound by a parental antibody" is withdrawn in view of the amendments to the claims.

8. The rejection of claims 33-37 under 35 U.S.C 112, second paragraph, as the being indefinite in the method of killing a malignant cell bearing an antigen is withdrawn in view of the amendments to the claims.

9. The rejection of claims 32 and 63 under 35 U.S.C 112, second paragraph, as lacking antecedent basis fro the phrase "a nucleic acid molecule" is withdrawn in view of the cancellation of the claims.

10. The rejection of claims 6-7, 9, 11, 17-20, 22-26, 28-30, 32, 35-40, 51-62 and 64-66 under 35 U.S.C 112, second paragraph, as being indefinite in the recitation "SS antibody" and "antibody E4" is withdrawn in view of the amendments to the claims.

11. The rejection of claims 6-7, 9, 11, 17-20, 22-26, 28-30, 32, 35-40, 54-55, 61-62 and 65 under 35 U.S.C 112, second paragraph, as the being indefinite in the recitation of amino acid substitutions at specific positions in antibody SS is withdrawn in view of the amendments to the claims.

12. The rejection of claims 6, 9, 11, 17-20, 28, 32, 36-37, 51-54, 56-61, 63-64 and 66 under 35 U.S.C 103(a) as being unpatentable over Chowdhury et al in view of Wagner et al and Schier et al and Pastan et al is withdrawn in view of the amendments to the claims.

13. The rejection of claims 6, 9, 11, 17-20, 51-54 and 56-59 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 9-31 of US Patent 6,809,184 B1 as evidenced by

Figure 1 in view of Chowdhury et al and Wagner et al and Schier et al and Pastan et al is withdrawn in view of the cancellation of the claims.

14. The rejection of claims 6, 9, 11, 17-20, 51-54, 56-59, 64 and 66 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 9-14, 18, 20, 24, 26 and 30-31 of US Patent 6,083,502 in view of Chowdhury et al and Wagner et al and Schier et al and Queen et al is withdrawn in view of the cancellation of the claims.

Response to Arguments

15. The rejection of claim 31 under 35 U.S.C 112, second paragraph, as lacking antecedent basis ~~fro~~ for the phrase "a nucleic acid molecule" is maintained.

The response filed 8/31/05 has been carefully considered, but is deemed not to be persuasive. The response states that claim 31 has been amended to provide appropriate antecedent basis. In response, claim 31 has not been amended and it remains unclear which nucleic acid is being referred to by the phrase "a nucleic acid molecule".

16. The rejection of claims 1-5, 8, 10, 12-16, 21, 27, 31, 33-34 and applied to newly added claims 69, 71-79, 81-84, 86-87 and 89 under 35 U.S.C 103(a) as being unpatentable over Chowdhury et al in view of Wagner et al and Schier et al and Pastan et al is maintained.

The response filed 8/31/05 has been carefully considered, but is deemed not to be persuasive. The response argues as previously argued, stating that the

SS scFv of Chowdhury et al is a high affinity antibody and the teachings of Wagner et al would not have suggested that antibodies which have been selected for high affinity through artificial process of phage display can undergo further increases in affinity through mutations in CDR hotspots and the ordinary skilled artisan would likely conclude that antibodies selected by phage display, and displaying the affinity reported by Chowdhury had already undergone mutation at these hotspots and obtained whatever benefit was available from such mutations. In response to this argument, Chowdhury et al teach that antibody SS was produced by immunization and selected for binding to mesothelin (see page 671), wherein the selection or panning was performed to enrich for mesothelin binding phage. Chowdhury et al do not teach that antibody SS had undergone affinity maturation or that affinity maturation would not yield any additional increases in affinity, nor does Chowdhury et al teach mutations within CDR hotspots in antibody SS or that further mutations within such CDR hotspots would not provide an additional increase in affinity. In fact, Shier et al teach a scFv having approximately the same affinity (Kd of 16nM) as that of antibody SS (Kd of 11nM) and CDR focused mutagenesis, particularly in CDR3 yielded a scFv with a 1230-fold increase in affinity (see page 552). Further, Schier et al teach that quantitative delivery of scFv to tumor is inadequate to provide therapeutic dosimetry and engineering higher affinity antibodies (i.e., scFvs) makes greater delivery possible. Thus, there would be an advantage to increasing the affinity of antibody SS, allowing greater delivery of therapeutic moieties to the cancer cell surface antigen, mesothelin, which according to

Chowdhury et al "represents a good target for antibody-mediated delivery of cytotoxic agents." (see abstract), particularly the cytotoxic agents according to the teachings of Pastan et al. Thus, one of ordinary skill in the art at the time the invention was made would not have assumed that the mere selection or enrichment of mesothelin specific antibodies by panning a phage library of scFv produced from the spleens of immunized mice had already undergone affinity maturation in CDR hotspots and further mutagenesis would not yield an additional increase in affinity in view of the teachings of Schier et al, providing evidence, motivation and a reasonable expectation of success that such additional increases in affinity are attainable.

The response argues the teachings of Schier et al stating that Schier was aware of the teachings of Wagner et al and despite this Schier teach a "mutagenesis strategy for efficiently increasing antibody fragment affinity" (page 562, left column) and it does not include focusing mutations on hotspot motifs. The response also states that according to the teachings of Schier et al, mutagenesis should be directed to VL and VH sequentially, and modeling should be used to identify CDR residues that are likely to have a structural role as these residues are conserved, leaving at most four to five residues to be completely randomized. Thus, applicant concludes that despite their knowledge of Wagner, the Schier authors do not teach restricting mutations to the residues encoded by RGYW or AGY hotspots, but rather randomizing, at one time, four or five residues in a CDR that are not identified as having a structural role. Applicant reminds the examiner that the teachings of the prior art must be considered "as a

whole" (MPEP 2141.02). In response to applicant's arguments, the examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art . In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In this case, the teachings of Schier et al indicate a correlation between significant sequence variability at certain CDR residues corresponding to the location of mutations of higher affinity scFvs, while other CDR residues were more conserved and according to Schier these conserved residues appear to have a significant structural role in the variable domain, either in maintaining the main-chain conformation of the loop or in packing on the VH domain and Wagner et al teach that the biased AGY or serine codon usage in the CDRs (i.e., hotspots) has evolved to help target mutations to residues that could yield increased affinity and away from places where they are more likely to destroy the structural scaffold. Further, Schier et al discovered that three serine residues in the heavy chain CDR3, encoded by AGY were hotspots for substitutions, which increased affinity (see page 561, bottom of left column), suggesting to one of ordinary skill in the art that targeting CDR hotspots will likely yield increased antibody affinity.

Thus, there would be an advantage to targeting mutations to CDR hotspots. Applicant is reminded that the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983) (MPEP 2144). In response to applicant's argument that that the teachings of the prior art must be considered "as a whole", it is unclear to the examiner which claim limitations applicant feels have been disregarded by the examiner and applicant has not pointed to any such limitations.

The response also states that the present invention is nonobvious by the fact that sophisticated persons of skill in the art at the time the invention was made did not consider it obvious, as shown by the fact that they considered it worthy of publication in one of the most prestigious and highest impact scientific journals (i.e., Chowdhury et al, Nature Biotechnology, 17:568-572, 1999). In response to this argument, it is totally unclear what this argument has to do with the present rejection, since publication in a scientific journal is based on the scientific merits of the published work, whereas the criteria for patentability is entirely different.

It is noted by the Examiner, that applicant's response to the pending obviousness-type double patenting rejection over the '502 patent (Pastan et al; discussed below), submits evidence establishing common ownership between the present application and the cited '502 patent of the above obviousness

rejection, however, the disclosure of the earlier filed '502 patent continues to be prior art under 35 U.S.C. 102(e) because the present application was filed prior to November 29, 1999. See MPEP 706.02(l)(3)[R-2].

For these reasons the rejection is maintained.

17. The rejection of claims 1-5, 8, 10, 12-16, 21 and applied to newly added claims 69 and 71-78 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 9-31 of US Patent 6,809,184 B1 as evidenced by Figure 1 in view of Chowdhury et al and Wagner et al and Schier et al and Pastan et al is maintained.

The response filed 8/31/05 has been carefully considered, but is deemed not to be persuasive. The response argues essentially as above against the obviousness rejection and as such the examiners arguments/rebuttal above apply here as well and the rejection is maintained.

18. The rejection of claims 1-5, 8, 10, 12-16, 21, 33-34 and applied to newly added claims 69 and 71-79 and 81-83 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 9-14, 18, 20, 24, 26 and 30-31 of US Patent 6,083,502 in view of Chowdhury et al and Wagner et al and Schier et al and Queen et al is maintained.

The examiner acknowledges applicant's comments pertaining to 37 CFR 1.78(c), and the submitted evidence establishing common ownership between the present application and US Patent 6,083,502, i.e., attorney of record makes a

statement to the effect that the application and the reference were, at the time the invention was made, owned by, or subject to an obligation of assignment to, the same person (see page 26 of the response filed 8/31/05).

The response filed 8/31/05 has been carefully considered, but is deemed not to be persuasive. The response argues essentially as above against the obviousness rejection and as such the examiners arguments/rebuttal above apply here as well and the rejection is maintained.

New Grounds of Rejections

19. Claims 69-89 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

The response filed 8/31/05 has introduced NEW MATTER into the claims. Newly added claims 69-89 recite anti-mesothelin antibodies comprising the heavy and light chain CDRs of antibody SS as shown in Figure 1, wherein said anti-mesothelin antibodies comprise mutations within CDR hotspots as well as nucleic acids encoding said anti-mesothelin antibodies and a method of killing cells expressing the mesothelin antigen comprising administering the anti-mesothelin antibodies. The disclosure as pointed to in the response filed 8/31/05 does not provide adequate written support for the presently claimed anti-

mesothelin antibodies, which only comprise the heavy and light chain CDRs of antibody SS and in the context of just any framework sequences and having mutations within CDR hotspots. Further, newly added claims 69-71, 73-76, 78-82, 84-85 and 87-88 do not require or recite that the mutations are within CDR hotspots selected from AGY or RGYW, which is an essential element of the presently claimed invention. Instant claims 69-89 now recite limitations, which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in newly added claims 69-89, which did not appear in the specification, as-filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C 112. Applicant is required to provide sufficient written support for the limitations recited in newly added claims 69-89 in the specification or claims, as-filed, or remove these limitations from the claims in response to this Office Action.

Conclusions

20. Claims 35-37 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

21. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR

system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER